

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
LOUIS C. CULLMAN
PRESTON GATES & ELLIS, LLP
1900 MAIN STREET, SUITE 600
IRVINE, CA 92614-7319

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing (day/month/year) 19 JUL 2009	
FOR FURTHER ACTION See paragraph 2 below	
Applicant's or agent's file reference 51326-00019	
International application No. PCT/US04/34206	International filing date (day/month/year) 15 October 2004 (15.10.2004)
Priority date (day/month/year) 15 October 2003 (15.10.2003)	
International Patent Classification (IPC) or both national classification and IPC IPC(7): A61K 39/04, 39/02, 39/00, 39/38; C12 N 15/00 and US Cl.: 424/248.1, 184.1, 185.1, 192.1, 200.1, 234.1; 435/320.1	
Applicant THE REGENTS OF THE UNIVERSITY OF CALIFORNIA	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

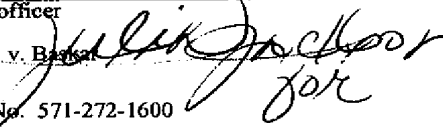
2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 872-9306	Authorized officer Padmavathi v. Baskar  Telephone No. 571-272-1600
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing
☐ contained in international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 36-42

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 36-42 are so unclear that no meaningful opinion could be formed (*specify*):

Claims from 36 are not numbered properly in accordance with Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>NONE</u>	YES
	Claims <u>1-7, 9, 11, 14, 16-32 and 34</u>	NO
Inventive step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-35</u>	NO
Industrial applicability (IA)	Claims <u>1-35</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Claims 1-7, 9, 11, 14, 16-32 and 34 novelty under PCT Article 33(2) as being anticipated by Horwitz et al U.S. Patent 6,471,967.

Claims are drawn to immunogenic composition and vaccine comprising recombinant BCG expressing the 30 major extra cellular non-fusion proteins of Mycobacterium tuberculosis.

Horwitz et al disclose immunogenic composition comprising a recombinant Bacilli Calmette-Guerin (BCG) having an extrachromosomal nucleic acid sequence comprising a gene encoding for a Mycobacterium tuberculosis 30 kDa major extra cellular protein, wherein said Mycobacterium tuberculosis 30 kDa major extra cellular protein is over expressed and secreted. Mycobacterium tuberculosis 30-kDa major extra cellular protein is over expressed and secreted such that an immune response is induced in an animal. Further, the nucleic acid sequence is under the control of a promoter that is not a heat shock promoter or a stress protein promoter. The prior art teaches Major extra cellular protein is a non-fusion protein. Vaccine composition is treated as an immunogenic composition as it contains the same components (see claims and examples). Recombinant Bacilli Calmette-Guerin (BCG) prototroph and auxotroph are considered as inherent properties of said BCG.

Claims 8, 10, 12-13, 15, 33 and 35 lack an inventive step under PCT Article 33(3) as being obvious over Horwitz et al.

Horwitz et al disclose an immunogenic composition comprising a recombinant Bacilli Calmette-Guerin (BCG) having an extrachromosomal nucleic acid sequence comprising a gene encoding for a Mycobacterium tuberculosis 30 kDa major extra cellular protein as discussed above but does not disclose a composition comprising 32kDa and 23.5kDa major extra cellular protein. However, the teachings of Horwitz indicate that recombinant BCG vectors expressing wide range of numerous species of microorganism (see column 6-7) would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the immunogenic composition with other proteins such as 23.5 and 32 kD with a reasonable expectation of success because it would have helped to induce immune response and thereby increasing immunogenicity of the composition. An artisan of ordinary skills would have been motivated in applying the teaching of Horwitz because the prior art suggests it would help the immunogenicity. One of ordinary skill in the art would know how to use multi proteins in a composition because multivalent vaccines for microorganisms are known in the art (columns 6- 8). The claimed invention is prima facie obvious in view of Horwitz et al absent any convincing evidence to the contrary.

Claims 1-35 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 27-35 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claims that recite vaccine are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because the disclosure does not teach the vaccine composition that could be used to prevent Mycobacterium, for example : M. leprae .

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.